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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OFFICE OF DEVICE EVALUATION

DENTAL PRODUCTS PANEL

Volume I

Monday, January 12, 1998

10:20 a.m.

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(202) 546-6666

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PARTICIPANTS

Dr. E. Diane Rekow, Acting Chairperson
Ms. Pamela D. Scott, Executive Secretary

PANEL MEMBERS

Dr. Janine E. Janosky
Dr. Mark R. Patters
Dr. Willie L. Stephens
Dr. Wilbert Jordan, Consumer Representative
Mr. Floyd Larson, Industry Representative

CONSULTANTS

Dr. Salomon Amar
Dr. Julianne Glowacki
Dr. Leslie Heffez
Dr. Howard Tenenbaum
Dr. Clarence Trummel

FDA STAFF

Mr. Timothy A. Ulatowski
Dr. Robert Betz
Dr. Susan Runner
Dr. Pei Sung

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C O N T E N T S

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P R O C E E D I N G S

MS. SCOTT: Good morning, everyone. Good morning and welcome to the Dental Products Panel meeting. My name is Pamela Scott and I am the Executive Secretary for the Dental Products Panel. I would like to welcome everyone to the meeting today.

If you have not signed in, please do so at the sign-in desk just outside the room. At the sign-in desk you will also find agenda booklets, if you have not already received one, and information on obtaining a transcript of today's meeting.

Meetings of the advisory committee panels are held only if there are issues or applications that FDA needs to or chooses to bring before the panel. Whether or not a meeting will be held is determined about two months prior to the tentative meeting date. When a decision is made the information is made available through the FDA Medical Advisory Committee Hot Line. The phone number for the hot line is 1-800-741-8138 or 301-443-0572. The code for the Dental Products Panel is 12518.

I would now like to introduce the members of today's Panel. Acting as our Chairperson for today is Dr. Diane Rekow. She is the Chairperson of the Department of

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Orthodontics with the University of Medicine and Dentistry of New Jersey.

We also have Dr. Janine Janosky. She is Assistant Professor with the Department of Family Medicine and Clinical Epidemiology, School of Medicine at the University of Pittsburgh.

We also have Dr. Mark Patters, who is the Chair of the Department of Periodontology with the College of Dentistry at the University of Tennessee, and Dr. Willies Stephens, who is Associate Surgeon with the Division of Maxillofacial Surgery at Brigham and Women's Hospital.

Our consumer representative is Dr. Wilbert Jordan. He is Associate Professor of Internal Medicine and Family Medicine, and the Director of the AIDS Program at the King Drew Medical Center at Charles Drew University. Our industry representative is Mr. Floyd Larson. He is the President of Pacific Materials and Interfaces.

We also have with us today Dr. Salomon Amar. He is Associate Professor with the Department of Periodontology and Oral Biology at Boston University. We also have Dr. Julianne Glowacki. She is Senior Investigator with the Department of Orthopedic Surgery at Brigham and Women's Hospital. Also with us today is Dr. Howard Tenenbaum. He

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is Professor and Head of Periodontology with the University of Toronto, and he is also on the faculty of dentistry at the Research Institute at Mt. Sinai Hospital, and we have Dr. Clarence Trummel. He is Professor and Head of the Department of Periodontology with the University of Connecticut Health Center School of Dental Medicine. Also we have, sitting at our Panel, our Division Director, Mr. Tim Ulatowski. He is the Division Director for the Division of Dental, Infection Control and General Hospital Devices.

The next items of business are three statements that are to be read into the record. The first statement is the conflict of interest statement for the Dental Products Panel meeting, January 12, 1998.

The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of any impropriety. To determine if any conflict existed, the Agency reviewed and submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employees' financial interests. However, the Agency has determined that participation of certain members

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and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government. Waivers have been granted for Drs. Mark Patters, Julianne Glowacki and Salomon Amar because of their interest in firms which could potentially be affected by the Panel's decisions. The waivers permit them to participate in all matters before the Panel. Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would also like to note for the record that the Agency took into consideration another matter regarding Dr. Julianne Glowacki. Dr. Glowacki reported involvement with a firm at issue but on matters not related to the meeting agenda. Since the matters are unrelated to the issues of this meeting, the Agency has determined that Dr. Glowacki may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements

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or presentations disclose any current or previous financial involvement with any firm whose products they wish to comment upon.

Secondly, I would like to read into the record appointment of temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 20, 1995, I appoint the following people as voting members of the Dental Products Panel for this Panel meeting on January 12, 1998: Dr. Diane Rekow, Dr. Salomon Amar, Dr. Julianne Glowacki, Dr. Clarence Trummel, Dr. Howard Tenenbaum, Dr. Leslie Heffez. For the record, these people are special government employees and are consultants to this Panel under the Medical Devices Advisory Committee. I also appoint Dr. Diane Rekow to act as temporary Chair for the purposes of this meeting.

The above individuals have undergone customary conflict of interest review. They have reviewed the material to be considered at this meeting. Signed by Dr. Bruce Burlington, Director for the Center for Devices and Radiological Health, January 9, 1998.

Each Panel member has before him or her a folder that contains information pertaining to the issues to be

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discussed today. In addition, we do have reference copies of the PMA that are available. I would like to remind you that certain information pertaining to the device discussed must remain confidential. This includes manufacturing information and formulation. Please be careful when you are discussing the submission not to make public any confidential information.

I will now turn the meeting over to Dr. Rekow.

DR. REKOW: Thank you. Good morning. The Panel today is charged with making recommendations to the Food and Drug Administration regarding the pre-market approval application of OsteoGraf/CS-300, which is a bone filling and augmentation device intended for periodontal use.

Before we have presentations from either the sponsor or the FDA we have an open public hearing. So, at this time I would like to invite anyone from the public who would like to address the Panel to let us know who you are, and I would ask that all of these people that do address the Panel come forward to the microphone and, please, be clear. Everything is going into a transcription and the note-takers are dependent upon being able to keep up with how quickly you present your material, and we need to provide an accurate transcription of the proceedings of the meeting.

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In addition, we request that anyone who is making these statements, either during the public hearing or in the open committee discussion portion, disclose whether you have any financial interest in any of the medical device companies, before making your presentations, if you could please also state your name and affiliation and the nature of any financial conflict, if any.

Is there anyone who would like to address the Panel who is here this morning?

(No response)

I will ask one more time just to make sure. Hearing no people from the public who are interested, we can then begin taking up the issue of the pre-market approval application by CeraMed Dental, L.L.C., on their product, OsteoGraf/CS-300. We will proceed with the open committee discussion. We will have presentations first by the sponsor of the PMA and at the end of those presentations, please remain at the podium for a little while so that we can ask you some questions. Could you also help us by identifying who you are and what your position is? That helps us, as the Panel members, to keep track of what is going on.

Introduction

DR. TOFE: Good morning. My name is Any Tofe. I

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am the President and CEO of CeraMed Dental. On behalf of CeraMed Dental, I would like to thank the FDA and members of the Panel for allowing us to present this summary and supporting information about the OsteoGraf/CS for the treatment of osseous defects related to periodontal disease.

At this time, I would like to pass out some hard copies of the presentation this morning to the members of the Panel and the FDA. The presentation will begin with an outline of what we are going to be talking about, and the presentation outline will start with an introduction and identification of the CeraMed Dental associates, our clinicians, our consultants, a very brief background on our company, then some concepts on how we go about looking at bone replacement graft materials, what type of models and what our development objective is, and then look at actually the OsteoGraf/CS itself and how it is manufactured, its components and the finished product, the OsteoGraf/CS.

I will do those three sections. We will then move to section four, the actual results of the multiclinical trial, which will be presented by Dr. Yukna, and he will go through the complete design and protocol objectives. I will finish up with our conclusions from the PMA.

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From CeraMed you have myself, the President and CEO, present here. We have Mr. Adarsh Sogal, who is the manger of R&D development and is responsible for much of the analytical methodology for looking at the P-15 in the OsteoGraf/CS; Mr. Mark Bowerman, manage of quality assurance and regulatory, responsible for regulatory aspects, GMP and Mr. Bowerman is also responsible for the just completed PMA inspection in which we have had no items identified by the FDA; finally, Andrew R. Tofe, a student intern at Colorado State University, who was charged in the last three months for coordinating documentation between the FDA and CeraMed Dental.

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The clinicians involved in the multicenter clinical trial were Dr. Ray Yukna, from LSU, the principal investigator; Dr. Jack Krauser, who is here present with us and is available for any questions regarding his clinical experience with the OsteoGraf/CS and, fourthly, Dr. Donald Callan, of Little Rock, had a previous commitment and was not able to attend.

Dr. Yukna's expenses have been fully paid by CeraMed Dental for this meeting. Dr. Krause has not been reimbursed for any cost at this meeting.

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We also have a number of consultants ready to address any specific issues raised by the Panel. We have Dr. Rajendra Bhatnagar, the Chairman of Bioengineering Graduate Program, Professor of Biochemisty and Biology, Bioengineering and Stomatology at UCSF at California. He is basically the inventor and developer of the P-15, this peptide. Dr. Barrett Jeffers, Director of Biostatistics, from the University of Colorado. He is our outside consultant reviewing the clinical design and analysis of the data from the multicenter clinical trial, and Miss Jyll Little, from Advanced ChemTech, the manufacturer of our peptide, to assure compliance with CGMP.

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CeraMed is located in Lakewood, a suburb in the western foothills of Denver, Colorado. The facility manufactures replacement graft materials in full compliance with FDA quality regulations, GMP, and we are ISO 9000 certified. Our facility is approximately 10,000 square feet, and right now we employ 31 full-time employees.

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The genesis from our company really comes from Coors, the brewery. In 1983 Coors Biomedical Company was

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formed, and in 1987 the name was changed from Coors Biomedical to CeraMed, meaning ceramic medicines. In 1990 there was a management buy-out and continued growth through 1996, when we realized that if we would continue our growth we would have to develop a relationship, a joint partner, and we did a joint venture with Dentsply International of York, Pennsylvania.

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We have been around for a long time, as the genesis showed you. In fact, in 1985 we introduced our first product, a dense hydroxyapatite, followed by a control matrix. The xenografts were introduced to the U.S. market in 1990, following most recently, last year, with a block form of the particulate material and now we are moving to OsteoGraf/CS-300, hopefully, in 1998. The xenograft is basically an improvement upon the alloplast and we look at this next generation, an improvement upon the xenograft.

So we have been around a long time. We have been doing grafting materials. That is our focus. The only thing CeraMed Dental does is develop and manufacture bone replacement graft materials.

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Let's look at the concept of bone replacement

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graft materials. The gold standard -- the ideal bone graft is a viable implant of autologous bone that restores mechanical and cellular function in the new location. So what we are looking at is autologous bone, and what we look at is a two compartment model where the inorganic part is basically a skeleton, a skeletal scaffold, and the organic compartment is responsible for cell attraction, attachment, stimulation and differentiation.

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We talk about a two-component model, looking at the inorganic component and the organic component, the scaffold and the cellular function. We see that the autograft really is the only one that gives us a dark check in both parts. It gives us both components as a substitute. So, we now start looking at the other types of graft materials which are presently on the market. We look at the allografts and we look at DFDBA, demineralized, freeze-dried bone allograft. Obviously, when we say the word "demineralized" we are removing the calcium phosphate so we are looking at just the organic compartment and we have a check for the organic compartment.

On the allograft we also have available today freeze-dried bone allograft. It has not been demineralized.

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There, clearly, we have the skeletal scaffold and we have an open part over here because there is some question about the cellular efficacy related to the organic part of allografts.

If we look at the alloplasts, the HAs, the glasses, we see that both of them only give us a check in the inorganic compartment. If we look at the xenografts, we see that they only give us a check in the inorganic. Even the enamel matrix has a an organic substitution but lacks the skeletal part. So, what we see over here is basically one check and what we are trying to accomplish is to look at both compartments.

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So, our objective was to find a substitute for the autograft that gave us an inorganic component. So, our objective was to develop a bone replacement graft that closely mimics the model of autologous bone. It is expected that such a product would provide a significant improvement over current products and, thereby, provide a significant clinical benefit. So, we are trying to find out if we can substitute for the inorganic component and if we can substitute for the organic component.

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So let's look at the OsteoGraf/CS and see how that

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accomplishes that goal. The way we look at it, trying to bring both components together, we go back to our model of an inorganic component and organic component, and we look at the inorganic component, looking at it as the calcium phosphate and we will show you how that relates to OsteoGraf/CS in a second. We look at the organic component and how that is primarily Type-1 collagen, and we will show you how that relates to P-15. Then we bring both of these together and we have the OsteoGraf/CS-300.

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So, let's look at each one of these individually and see how these components make up the sum. So, let's first focus on the OsteoGraf/N-300. OsteoGraf/N, where "N" stands for natural and the 300 simply means the mean diameter in microns of the particle size, is produced from bovine.

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It is a xenograft, naturally derived HA, sourced from animals in the U.S., according to U.S. D.A. specifications, totally deproteinated with all the organic removed, and meeting the specifications of ASTM F1581-95, which has been defined as the specifications to assure you have removed all the organic.

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To show you the similarity to the autograft, we just show you some x-ray diffractions, and the only thing that is important that we are looking at human cortical and human cancellous, and the lines should all line up. In other words, we have the same crystalline type structure as we do with human bone.

The same is true with the infrared spectroscopy. We have a classical carboxyl group which is in human bone but the rest of them all line up, in essence, showing us that the xenograft is in essence a good model for the autograft.

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What about the safety of the OsteoGraf/N? Well, obviously it is manufactured in complete compliance with FDA quality regulations and ISO 9001 and, by the way, the ISO were the European standards. It meets all the tripartite biocompatibility testing, and it has actually been in the U.S. and marketed in the U.S. since January of 1991 under a 510(k).

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To date, approximately 92,000 grams of the OsteoGraf/N-300 has been marketed in the United States.

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There have been no MDR reports with this material -- a couple of minor complaints so I thought I would show them all. We have had a total of 9 since 1991. Clinicians said they remodel too slowly, three of them. Spilled vials accounted for 4 of the complaints. Moisture in the vial was 1. The last minor complaint was that the clinician said the radiopacity varied between the patients.

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Let's move on to the P-15, the organic component side. We looked at the N; let's look at the P-15, synthetic peptide development. Collagen accounts for approximately 30% of total protein mass in the body and provides for cell migration, cell binding and cell differentiation. We now know that the P-15 does the same thing.

There are nearly 20 types of collagen that are known to exist with Type-1 collagen, of course, being the predominant species, accounting for over 90% of the total collagen. Demineralization of the autograft leaves the matrix primarily Type-1 collagen, that is, demineralized, freeze-dried bone allograft.

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Type-1 collagen molecules have 3 alpha chains of approximately 1000 amino acid residues each. What P-15 is,

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is a linear peptide with a 15 amino acid sequence identical to the sequence contained in residues 766-780 of the alpha-1 chain. In other words, if our collagen is here, 1000 amino acid residues and we break this down and we look from residue 766 up to 718 and we count the number of amino acids, there are 15 of them and we wind up at 780, this is P-15, this part of collagen is P-15.

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What about the safety of the P-15? The best way to look at the safety is to really look at freeze-dried demineralized bone, but we are looking at a part of freeze-dried demineralized bone. As we all know, freeze-dried demineralized bone is almost entirely Type-1 collagen. The major amino reactive residues in freeze-dried demineralized bone are associated with the amino and carboxyl terminals and the triple helical region at the end portions. That is where the concerns are from amino reactivity. P-15 is a linear with a sequence identical contained to this alpha chain, over here. The 766-780 residue is in the central portion of collagen. It is over here, not in the antigenic regions associated with freeze-dried demineralized bone.

To give you some perspective, if you take the 15

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amino acids over the 10000 in the whole collagen chain, you have 1.5% of the alpha chain or 0.5% of the triple helix. The molecular weight of collagen, of course, is about 300,000 Daltons. The molecular weight of P-15 is 1400.

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P-15 is essentially a very small synthetic fragment of the alpha-1 chain of Type-1 collagen. Going back to the safety of demineralized freeze-dried bone, this is only a part of demineralized freeze-dried bone. To date, there are no reported adverse clinical reactions to demineralized freeze-dried bone, Type-1 collagen, as a bone replacement graft material in dental applications. There have been hundreds and hundreds of thousands doses of freeze-dried bone used without a problem.

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To put it on a gram basis, an equivalent dose, 1 gram, that a clinician would give to a patient of demineralized freeze-dried bone, which is obviously Type-1 collagen, produces an exposure to the patient of 1,000,000 micrograms of collagen. The P-15 is about 10,000 times less than what the patients get if they were using demineralized freeze-dried bone.

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I just show this -- we make P-15 by classical synthetic solid state chemistry, synthetic peptides. This is what they call a peptide synthesizer.

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The quality control associated to show purity and identity of all the various tests we do -- sequence analysis, purity of reverse-phase HPLC and so forth, telling us that we have a product which is greater than 95% pure.

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So now, what we have done, we have looked at the inorganic component; we have shown OsteoGraf/N. We have looked at the organic component and shown that the Type-1 collagen was best represented by the P-15. Now we bring them both together and we have OsteoGraf/CS, the "CS" for "cell sticking." So OsteoGraf/CS is a high purity, radiopaque, natural hydroxyapatite bone replacement material, in other words, the OsteoGraf/N with the P-15 as a synthetic peptide.

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What about the safety of the P-15? Obviously, both compartments are extremely safe but we still have to bring them together and do tripartite testing to assure biocompatibility and safety. So, what we are really doing

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is combining 1 gram of the OsteoGraf/N with basically 215 nanograms or 0.00000025 grams, and we bring these together and we form OsteoGraf/CS, then we go back and repeat the tripartite study.

We have shown with the tripartite study that the OsteoGraf/CS is non-hemolytic; that the OsteoGraf/CS is non-cytotoxic and non-mutagenic --

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-- with no systemic toxicity; no irritation/ toxicity; no sensitization. Macroscopically, we see no irritation. Microscopically, we see some expected cellular activity.

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So, from looking at all the safety data we come to the conclusion that the long-term safe use of OsteoGraf/N bound with a minute amount of the synthetic small chain linear peptide, the P-15, representing the non-immunoreactive portion of the Type-1 collagen, yielded the expected tripartite conclusion of safety for the OsteoGraf/CS-300.

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We were satisfied we completed all the safety issues. It is clearly a safe product. But now comes the

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question which, from our development and R&D standpoint, we want to look at. Is the matrix, the OsteoGraf in itself the matrix which the P-15 was put onto, itself responsible for the effect I am going to show you and not the P-15 component, in other words, the control?

The second question, does the adsorbed P-15 component have a cell stimulation effect? Now, to us the word "stimulation" means cells attraction, differentiation, attachment.

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What I am going to do now is sort of give you a very brief overview of a number of studies which were done addressing this question of cell migration, the question of attachment, migration, differentiation.

This first study was published by Dr. Qian and Dr. Bhatnagar. It was published in The Journal of Biomedical Materials Research, in 1996. Those studies were using dermal fibroblast with OsteoGraf/N and then the identical OsteoGraf/N to which simply the P-15 had been added. So, in essence, everything was exactly the same with the exception that one had P-15 and one did not have P-15.

So, looking and comparing the two by light microscopy, we see that over the control, the OsteoGraf/N

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matrix we had enhancement in basically attachment and migration.

If we looked at the macromolecular synthesis in the formation of DNA and protein by radio label studies, we found enhancement in migration and attachment.

If we looked at SEMs comparing the two we saw enhancement and migration, and se stained for alkaline phosphatase for the two and we saw enhanced differentiation.

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This is another study. We are now going from dermal to using PDLF fibroblast cultures but the same types of studies by the group at UCSF. This was a paper presented at the IADR and also Dr. Sadeghi's thesis.

Again, we show enhancement looking at the molecular synthesis of protein and DNA. We looked at enhancement of CS-300. With SEM, the same thing, we showed enhancement in attraction and migration.

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Another study recently from the LSU group with Dr. Moses -- SEM observation of cell spreading. We show again, comparing the two, identical matrices with the only thing being different is the peptide, the P-15. We showed enhancement in binding to surfaces, attraction, spreading.

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We showed enhancement with the peptide.

What do I mean by "enhancement?" Well, this is without the peptide, this is with the peptide. What do I mean by "differentiation?" Alkaline phosphatase, this is the particle without the peptide, staining with the peptide.

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We then did a rabbit study, in New Jersey with Dr. Parsons, to look at ingrowth in a delayed cranial defect model, ingrowth of the "N" and the CS, the same, exact matrices, with the only major difference in the migration in the enhancement or the migration into the center of the defect. Here is the histomorphologic analysis with the same exact matrix, also showing enhancement.

This is illustrated in their study. That is without the peptide; that is with the peptide. Interestingly, in the center of the defect where you would not expect to see any type of really new osteogenesis or new bone formation over here without the peptide and every particle in the center, by simply adding the P-15, we have new bone formation.

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So, our conclusions from our <u>in vitro</u> and our <u>in vivo</u> studies using the identical matrix, the

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OsteoGraf/N-300, with and without this P-15 showed enhanced cellular stimulation with the addition of the P-15. So we were satisfied that we have answered the technical question with respect to did the P-15 make a difference. It clearly made a difference.

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Now what we have to do is address the clinical question, the clinical utility of OsteoGraf/CS. That is, its applicability; its comparison to clinical procedures presently utilized by the clinicians in the management of intrabony periodontal defects. With that, we will get to the multiclinical trial and I would like to turn the podium over to Dr. Yukna.

Clinical Trials

DR. YUKNA: Good morning. I am Dr. Ray Yukna, Professor and Head of the Department at LSU Dental School, in New Orleans. As Dr. Tofe said, I am supported to be here before the FDA Panel with travel expenses. I have no other financial interest in this company as far as owning any stock or rights or anything like that.

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I was privileged to be asked to be the principal investigator for a multicenter clinical trial to evaluate

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this material in patients. The design was such that we wanted to compare the test material, which in the PMA submission was called ABM P-15, a combination as a bone replacement graft material in human periodontal defects.

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The working hypothesis was that the test material, the OsteoGraf/CS, would be at least as safe and effective as demineralized freeze-dried bone allograft and more effective than surgical debridement alone.

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We felt that the preclinical in vivo and in vitro data allowed us to go to a clinical transition because that data, as you have seen from Dr. Tofe, was extremely favorable for the activity of the material. There appeared to be very little downside as far as patient risk because of the safety profile of the P-15, and three independent IRBs approved the clinical protocol for enactment at their various centers. The other clinical advantage would be the potential biological advantage that this material might have over currently available bone replacement graft materials.

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In order to set up the clinical protocol we needed some baselines in order to establish clinical norms of

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expectations. In overall periodontal literature there are some landmark values from the vast variety of types of regenerative procedures and techniques in studies that have been done. In general across the board, the percent defect fill of the osseous defect or the bone loss area is about 60-70%. The clinical probing attachment level gain was about half to three-quarters of a millimeter, and probing depth or pocket depth decrease ranges between a millimeter to a millimeter and a half.

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More specific to the study we wanted to perform, we looked for controlled, intra-patient, reentry studies that utilized the similar types of materials that were going to be used in this project. In the periodontal literature, as you can see from this, for demineralized freeze-dried bone allograft, surgical debridement or hydroxyapatite type materials there are studies, ranging from 10 to 15, that had this sort of study design. In those studies, the mean of patients used ranged anywhere from about 10 to 15 or 16. As you see, when we developed our protocol we exceeded that mean patient value by about 2X.

In these particular studies the percent defect fill was less than the norm across the board, being less

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than 60% for both of the grafting materials and about 25% for the surgical debridement. Relative defect fill, used as the frequency of responses to a treatment, ranged from about 70% for the bone material to about 60% with the synthetic material and about 30% with debridement. Clinical probing attachment level gain was anywhere from 1.2 mm to 1.8 mm, and probing depth decrease was from about 2.5 mm to 3 mm. So these became the norms that we wanted to compare our material against as the results became available.

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The protocol design objective was to compare the OsteoGraf/CS to demineralized freeze-dried bone allograft that is considered to be the gold standard in periodontal therapy today. It served as a positive control and was used basically for determination of the "n" for our study. We also wanted to compare it to surgical debridement as a standard negative control.

We chose demineralized freeze-dried bone allograft as the positive control because it is far and away the most commonly used bone replacement graft material, with the most clinical data available to establish an adequate "n" and to compare clinical significance or clinical utility.

The working hypothesis was to prove equivalence to

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the gold standard graft material, and this gold standard label was given to it by the Annals of Periodontology, which are based on the American Academy of Periodontology Workshop held a couple of years ago.

There was no substantial data base available for comparison of the OsteoGraf/CS with the OsteoGraf/N base material so we really had to focus on the OsteoGraf/N base material. So we really had to focus on the most commonly used gold standard as our positive control.

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We used surgical debridement as a negative control because it is, again, far and away the most commonly used non-grafting procedure with, again, clinical data to establish an adequate "n" to compare clinical utility. We wanted to prove superiority to this surgical debridement therapy in order to show effectiveness of the CS, and it is a classic reference treatment for comparison with regenerative treatment such as bone replacement graft materials in the periodontal literature.

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So to review, our outcome would be considered successful if the test device, the OsteoGraf/CS, was greater than or better than or equal to the positive control for

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these three primary clinical parameters, and greater than or better than the negative control.

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The protocol design was one of a prospective, controlled, monitored, multicenter design, utilizing calibrated, separate, blinded examiners at each center. There were set inclusion and exclusion criteria, and it was intra-patient or same mouth 3-treatment arm design rather than a parallel design. This allowed us to be much more efficient in utilization of subjects to gain statistically and clinically significant data with the same mouth or intra-patient self-control design.

The test material is the CS-300. The demineralized freeze-dried bone allograft is the positive control. It was all achieved or obtained from the same donor, and it is aseptically processed by a tissue bank that complies with AATM standards, and surgical debridement was the negative control.

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The reentry time chosen for evaluation of the hard tissue or bony changes was 6-7 months, and the total evaluation time for soft tissue changes was 12 months. This was based on work by myself and co-workers and Wenzel et al.

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They both showed that there was no change between 6 months and 12 months in these types of studies.

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In setting up the protocol we also had the help, besides Dr. Jeffers who is here today, of two of my fellow faculty members at LSU in designing the statistical arm of the protocol and determining the "n" determinations.

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The inclusion/exclusion criteria were limited to adult periodontitis, meaning patients who were at least 35 years old. This by far and away the most prevalent type of periodontal disease in our country and in the world. Each patient had to have 3 intrabony defects each for treatment and evaluation. They had to be similar in depth and dimension.

We restricted the risk factors that might complicate wound healing. We only enlisted non-smokers, non-diabetics and patients with no other medical or social factors that may compromise healing. In addition, all of the subjects who were finally enlisted in the surgical phase of the study had to exhibit good oral hygiene so they could maintain the results of therapy.

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Now, this is kind of a scheme of how the protocol development went. This started over 3 years ago with meetings with the FDA to discuss and develop the protocol, to establish an appropriate "n", to establish acceptable controls, and the protocol was finally, after several meetings and amendments, accrued in September of '95 and the study was actually initiated about 2 weeks later.

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On the right-hand screen you see the total study time. It took a little over 20 months, with the first patient treated in October of '95 and the last 12-month evaluation performed in June of '97.

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Prior to the study start, we felt it was extremely important that we have calibrated examiners. We accomplished this by centralizing the calibration initially against myself, as the project director at LSU, where the examiners from each center came and were calibrated on several patients, both inter- and intra-examiner calibrations. Then prior to the start of the study at each site, as the project director I went and reestablished calibration with the examiner in their own environment.

It ended up that we had concordance, meaning no

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difference in measurements, either subjective or objective, between 88-94% across all the examiners, and within 1 mm or 1 score for the subjective values, or better than 90% among all the examiners.

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The age range is reflective of a typical periodontal practice in that the patients had to be at least 35 years old and were sort of on a bell curve, if you will, in the age groups listed.

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In addition, there was almost an equal distribution of male and female subjects in the study.

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In addition, the number of patients per center is listed here. Center 1, at LSU with myself as the principal investigator; Dr. Krauser, in Florida; Dr. Callan, in Arkansas. The patients initially treated were 36. We had a handful of dropouts before the 6-month evaluation point for the bone changes, virtually equally distributed among the centers. There was 1 additional dropout between 6 and 12 months, which yielded 31 subjects, which was greater than our initial "n" of 22 at 6 months and 30 at 12 months.

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The treatment procedures used followed typical periodontal surgical routines, in that the patients initially underwent initial preparation and reevaluation procedures to make sure the tissues responded to the initial scaling and root planing and that the oral hygiene was satisfactory. Then full thickness flap development and defect debridement was performed. Root debridement was accomplished with mechanical means only, not with any chemical adjuncts. Then once all of the defects and root treatment was completed, the treatment of the defects was randomized according to a random code with 1 of the 3 treatment modalities tested. All 3 were used in each patient.

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Following application of the materials, as appropriate, the flaps were replaced and sutured with primary closure where possible. Periodontal dressings were used in almost all cases. As per normal periodontal surgical regimes nowadays, doxycycline antibiotic was prescribed for about 10 days, nonsteroidal anti-inflammatories for a few days, and antibacterial rinses for the first few weeks following surgery.

The patients were followed very frequently

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postoperatively, weekly for the first month and monthly for the next 3 months, and then placed on typical periodontal 3-month recall.

The reentry surgery for bone evaluation was performed at between 6-7 months and soft tissue evaluations were completed at 12 months.

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These are the results of the study. The first thing we will talk about is the hard tissue changes or the bony defect changes that were determined at the surgical procedure initially and at the reentry surgery. These are the 3 treatment arms used, the CS-300, demineralized freeze-dried bone and the debridement.

The original defect depth means were essentially similar and not significantly different among the group to start with. Some were in the 3.5-4 mm range. The residual defects became shallower because treatment was successful. In fact, all 3 treatment arms achieved a positive clinical result in reducing the bony defect.

There were significant differences across treatment arms where the CS-300 was superior to the demineralized freeze-dried bone and the debridement for residual defect depth, for the amount of defect fill in

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millimeters, for the percent of defect fill, for the amount of bone adsorption from the crest of the bone and for the percent defect resolution.

Of significant to me is this figure of 72%, which is higher than virtually any other study reported in the literature for percent defect fill.

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In looking at this data a little differently and dividing it up by quintiles, we kind of see a pattern develop in which the CS-300 consistently gave more improved defect fill percentages, with the majority of them above 60%. The demineralized freeze-dried bone was more evenly distributed by quintile and, not surprisingly, the debridement had a majority of their cases at the 40% or less defect fill. So, again, the pattern with CS-300 was clinically and statistically superior to the other two treatments.

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Another way to typically look at this data in the periodontal literature is to look at what is called relative defect fill. What that says is what is the frequency of times that the response is of certain percentage defect fill, and it is typically broken up into

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poor, moderate, good and excellent results and what percent defect fill was in a given or in a given defect.

The key here is to take these positive results, greater than 50% or greater than 90%, and you see that in the CS-300 the frequency of positive results was almost 90%. With demineralized freeze-dried bone the frequency was about 60%; with debridement it was about 40%. So, again, head and shoulders above the other two. The CS-300 showed a much more consistent improvement in the osseous defects and the frequency of a positive result.

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The soft tissue changes reflect both the 6-month and the 12-month probings. Again, all 3 treatments accomplished pocket depth reduction significantly from the presurgical. Of note also is that there was no significant change, almost no arithmetic change between the 6-month and the 12-month data for all 3 treatment arms. There were no significant differences in pocket depth changes across the treatment arms when compared to each other.

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We looked at clinical probing attachment level gain at both 6 months and 12 months. There was some slight improvement in attachment level gain as time went on but not

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significantly so from the 6-month standpoint, and there was a significant difference between the CS-300 and surgical debridement in attachment level gain from the 6-month standpoint. There was again some slight decrease in gingival recession as time went on, with no significant differences among those either.

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In center 1, because of the reconstructive philosophy of the therapist in that center, we recorded the defects at reentry that we felt required additional grafting that would benefit from that treatment. You can see that, again, with the CS-300 only 2/14 defects required additional treatment, while over half of the demineralized freeze-dried bone, and over half of the debridement defects were felt to require additional grafting for completion of treatment.

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Safety-wise, there were no untoward effects reported or patient complaints related to either of the 2 bone replacement graft materials used, either the OsteoGraf/CS or demineralized freeze-dried bone. Both of these materials appeared to be clinically well tolerated by the periodontal tissues.

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What I would like to do now is go through some clinical cases that demonstrate the response of the bony defects to the use of the CS-300.

On your left screen will be the initial defects, and for your orientation, this is one of the bicuspid study defects that received the CS-300. It is about 5 mm deep from the top of the bone to the bottom of the hole in the bone. After proper preparation the CS-300 is placed in the defect. The flaps are covered. Six months later, when we go back to look at this same spot, it is very apparent that something has happened to the hole in the bone, and it is filled with something that resembles, clinically at least, bone material.

(Slide)

An anterior bony defect that wraps around this tooth rather significantly. Again, OsteoGraf/CS-300 is placed. At the reentry, you can see the changed in the topography of that bone with something that has filled in and repaired those irregularities and the hole in the bone. I might add that all of these cases that I am showing you, the clinical radiographs, are samplings of all 3 treatment centers.

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An upper bicuspid tooth, again, OsteoGraf/CS-300 was placed and 6 months later repair and fill of that defect.

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An anterior tooth, just to show you different places in the mouth. CS-300 in place and 6 months later, again, reconstitution of the shape of the alveolar ridge by filling of that defect.

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A lower anterior deep lesion on this bicuspid tooth. Six months later you would be hard-pressed to know that there was a lesion there to start with.

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Now, radiographically we have some evidence of the incorporation of retention of the CS-300. Again, this is the tooth in question, here, with this defect, bone loss distal of the first bicuspid. This is at the time of grafting.

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This is 6 months later.

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This is 12 months later. It shows incorporation, retention, perhaps remodeling of the material and resolution

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of the defect.

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A lower bicuspid tooth that you saw a clinical case of earlier, with about a 4.5 mm defect at the time of graft placement with the CS-300. Six months later, retention of most of that, almost complete residual defect resolution, and 12 months later further consolidation and retention of the material and appearance of incorporation and healing bone.

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A lower bicuspid tooth again, about a 6 mm defect; material in place.

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Six months later the material is still retained.

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And 12 months later a rather complete resolution of this bony defect, with maintenance of the adjacent bone as well which is key in this type of procedure.

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Upper bicuspid -- this provides us 2 examples. They were adjacent defects, with the CS-300 and surgical debridement defect here. At the time of graft placement and, obviously, no graft was placed in the adjacent defect;

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6 months later retention of the graft material; retention of the same defect shape on the debridement side, and 12 months later showing incorporation, resolution of the defect and the treated grafted area, but not on the surgical debridement side.

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On the anterior, again a similar picture. A defect here, about 3.5 mm.

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This is at 6 months and this is at 12 months. Unless you knew this was treated, you would not know that there had ever been periodontal disease at that site radiographically.

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Another upper example of a bicuspid tooth, number 13. This is at 6 months --

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-- and at 12 months, again, with a rather complete resolution, natural appearance radiographically. It looks like bone regeneration or bone formation in that defect.

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So the conclusions from the clinical study, based on the data and the pictures we have shown you, are that the

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CS-300 met or exceeded the prospective criteria we established for the multicenter clinical study.

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It was greater than, better than or equal to the demineralized freeze-dried bone in percent defect fill and better than debridement. Attachment level gain at both 6 and 12 months was greater than or equivalent to and greater than. Pocket depth decrease at 6 and 12 months was greater than or equivalent to and greater than. So this met all of the criteria we established to establish clinical effectiveness and clinical utility.

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So overall conclusions, I feel as the principal investigator, along with my co-investigators, that the OsteoGraf/CS-300 obviously performed the best among the 3 treatments tested and shows promise for improved clinical results in human periodontal bony defects based on the criteria for percent defect fill, attachment level gain and relative defect fill.

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In addition, the CS-300 appeared to be very effective and very safe, with no untoward results whatsoever. The test material results were both

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statistically and clinically significant, and the CS-300 met the criteria of the protocol and justified the statistically derived sample size to prove both its clinical utility, safety and effectiveness.

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So to just kind of review what we are focusing on, the historical criteria from similar studies, meaning controlled, intra-patient, self-controlled clinical studies with reentry, the percent defect fill ranged from 50-56%, almost 20 percentage points better. Attachment level gain was similar, which was one of our criteria. Pocket depth decrease was similar, which was one of our criteria. Relative defect fill was again 20 percentage points better than what has been in the literature for demineralized freeze-dried bone or plain HA materials.

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So the overall advantages of CS-300, as an investigator and clinician, I felt that very superior consistent clinical results were achieved. It provides a much more consistent material for grafting rather than tissue bank materials which, as we now know from the literature, vary greatly in their quality. It avoids any potential safety issues with allograft of tissue bank

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materials and, I feel, provides a major biologic advance in the arena of periodontal regenerative therapy using bone replacement grafts.

I would like to turn the presentation back to Dr. Tofe.

Conclusions from the PMA

DR. TOFE: Thank you, Dr. Yukna. I would like now to summarize our conclusions from the data that was presented today.

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First, the OsteoGraf/CS met or exceeded all prospective clinical efficacy parameters compared to the clinically relevant positive control of demineralized freeze-dried bone and the negative control, surgical debridement.

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The multicenter, 3 independent clinical sites, same mouth design, with positive and negative controls, provided a statistically valid determination of clinical efficacy.

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The in vitro and the in vivo animal studies showed enhanced efficacy with the synthetic peptide, the P-15,

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which was then validated, of course, with the clinical efficacy observed with the OsteoGraf/CS-300.

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Following the long-term use of OsteoGraf/N with the simplicity of a small linear synthetic peptide, the P-15, yielded the expected preclinical tripartite and the clinical safety observed in the OsteoGraf/CS clinical trial.

Upon completion of this clinical trial, the PMA was submitted to the FDA on December 23, '96. Shortly after that it was submitted to the HPB in Canada and then it was filed officially with the Food and Drug Administration on August 8, 1997.

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I would now like to summarize and respectfully request the Panel to recommend to the FDA that OsteoGraf/CS be approved for use as a bone filling material for intrabony defects and restoration of lost bone due to adult type periodontal disease.

On behalf of all of us, I thank you very much.

DR. REKOW: Thank you. Are there any questions that we have for the CeraMed people?

DR. PATTERS: I have a question for Dr. Yukna, if I could.

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DR. REKOW: Dr. Patters, could you state your name so that the transcriptionist will know who is talking?

DR. PATTERS: Sure. Mark Patters. Dr. Yukna, the site in Little Rock and the site in Palm Beach were private offices?

DR. YUKNA: Yes, they were.

DR. PATTERS: Can you tell us what methods you have to use in order to ensure blinded examiners when you operate in a private office?

DR. YUKNA: At each office one of the staff members, a hygienist in one and a dental assistant in the other, were the ones that were not involved in the treatment of those patients. They were called in at the time to simply take the measurements. That was set up with the examiners in the centers. They had to make the commitment to be able to do that.

DR. PATTERS: So, Dr. Callan and Dr. Krause were the surgeons but not the examiners?

DR. YUKNA: correct.

DR. PATTERS: Thank you.

DR. AMAR: Salomon Amar. For Dr. Yukna, I was just wondering, could you tell the Panel whether all the defects were either 3-wall defects or 2-wall defects, and

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whether or not there was any attempt at randomization of the defects?

DR. YUKNA: We don't have exact data. Almost all of them were 2, 3-wall or 3-wall type defects. We didn't record that. That was an omission in the protocol. Randomization occurred. All of the defects were treated at a single session, and all the defects were debrided and root surface preparation completed, and then the randomization code was established for which treatment, and then it was simply measured then closed and followed from that point on. So the randomization was not by defect wall but the criteria of being at least 3 mm deep, osseous defect at least 3 mm deep and 3 of them in the same patient. It was at that point that the randomization occurred.

DR. AMAR: So there was basically the possibility that the sites that were determined for debridement could be 2-wall or 2-wall defects.

DR. YUKNA: It could be. There was a mixture and there was no predetermination made of which ones were going to receive which treatment. So, it was the luck of the draw. You know, I can't say that in each patient they were all exactly the same wall defects, but across the board there would probably be a balance among them. As far as I

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know from looking at all of the slides and all the radiographs, there were no true 1-wall defects that were treated. They were all some sort of combination of 2, 3-wall, maybe 1-wall components. So, it did vary within patients and among patients.

DR. AMAR: I have another question, not to you but probably to the sponsor, was there any attempt to determine the exact molecular area or molecular basis for cell attachment on the P-15? There are reports in the literature to suggest that there are an RGD sequences that mediate the cell attachment which I didn't see in the P-15. Is there any comment?

DR. TOFE: Yes, I would probably defer that question to Dr. Bhatnagar, who is probably the more experienced. I could answer but I would rather have Dr. Bhatnagar do it.

DR. BHATNAGAR: The area that we have identified, P-15, did not contain an RGD site. It was developed on the basis of my studies on the structure of collagen, looking at sites on collagen which have chemically perturbed sequences, and we were surprised to find that the domain that is contained in P-15 expresses a very unique kind of a structure. We have recently published that in The Journal

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of Biomedical Structure and Dynamics. This particular domain is quite non-polar. In that sense, it differs from all other peptides that bind cells.

DR. GLOWACKI: Julianne Glowacki. While you are up there, Dr. Bhatnagar, can you expand on that last statement? Is there something unusual about the sequence of the P-15 that gives it some tertiary structure? Do those small peptides refold in a triple helical configuration?

DR. BHATNAGAR: Actually, no. The small peptides themselves have smaller derivatives of P-15 to generate a very stable beta structure. The central part is GIAG, which seems to be the active part.

DR. GLOWACKI: And no aggregation then of individual --

DR. BHATNAGAR: There is no aggregation in this.

DR. GLOWACKI: And if I may ask Dr. Yukna some questions about the clinical presentation, was there any analysis done about the location -- the results as a function of the location of the defect? You commented during the case presentations about adjacent defects. Can you expand on that, whether that was taken into account? I guess not with regard to the randomization but a post hoc analysis to determine whether there was an influence of

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adjacent defects on the different treatment groups.

DR. YUKNA: The adjacent defects occurred rather infrequently, I think maybe half a dozen times. Just looking at that small group, it didn't seem to influence results. Obviously, if P-15 was going to migrate, it would have improved the surgical debridement site and essentially nothing happened in that site.

As far as other things, we did look at maxillary versus mandibular and anterior versus posterior and there were no differences. It was equal across the board as far as response.

DR. GLOWACKI: I think I understood the design to say that patients had to have at least 3 defects to be eligible for the study. In the situations where the patients had 4 or more defects, how were those other defects treated?

DR. YUKNA: In only one of the centers were some of those extra defects included. Then they underwent the same randomization. It happened to be center 2, and in that center 5 patients received an additional treatment of some sort, and that was almost equally distributed. There were 2 extra CS-treated, 2 extra DFDBA-treated and 1 extra surgical debridement-treated, again, just according to randomization.

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Then that data was meaned for that patient for statistical analysis.

DR. GLOWACKI: I see. I have a question for Dr. Tofe. For cell biologists the term "migration" has a very specific meaning and I would like to pin you down on what you mean by that, both with regard to the in vitro studies that you referred to when you used that term, as well as the in vivo.

DR. TOFE: Migration to me basically means movement across the field. So, in vitro for example, in the case of the rabbit we showed a further movement from the wall out.

DR. GLOWACKI: In vivo?

DR. TOFE: In vivo. In case of the in vitro, looking at the surface of the actual individual particles that we illustrated in the scanning electron microscope, we saw a few particles as opposed to having the whole field covered. That, to me, is migration.

DR. GLOWACKI: But in the abstract I think the word "spreading" was used for that.

DR. TOFE: That was in the Moses, correct, but in both the Qian -- you are correct, spreading, but my definition of migration is movement across the surface.

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DR. GLOWACKI: Across the surface of the particle.

DR. TOFE: Of the particle.

DR. GLOWACKI: Okay, not migration toward the particles --

DR. TOFE: No.

DR. GLOWACKI: -- which a cell biologist might think of in those terms. Thank you for the clarification.

DR. TENENBAUM: Dr. Tenenbaum. Some questions regarding the differentiation of the dermal fibroblasts. You used alkaline phosphatase as an indicator of differentiation. Could you explain what you mean by differentiation?

DR. TOFE: I will defer that to Dr. Bhatnagar.

DR. BHATNAGAR: We cultured dermal fibroblasts on the surface of hydroxyapatite particles that had been coated with P-15 in my laboratory, and very soon we began to see that the cells were assuming quite a different morphology. Both histologically as well as by staining procedures, these cells seemed to appear not to be fibroblastic any longer. The paper that is part of the PMA submission showed that we had alkaline phosphate induction in the presence of P-15. I don't know if I can talk about this work or not, but more recently we have looked at this issue again and we find that

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quite a few markers of bone are expressed in terms of gene expression, like osteonectine, and we also have evidence that BMP-7 osteogenine might also be induced in the system.

DR. TENENBAUM: And how did you demonstrate that those other bone-associated proteins were there or were being produced by those cells?

DR. BHATNAGAR: Looking at gene expression.

DR. TENENBAUM: One of the reasons I am asking is that some fibroblastic cells do express alkaline phosphatase. In fact, there is evidence that this enzyme is associated with phagocytosis of collagen. So, when I saw the data I was wondering whether perhaps the presence of P-15 was inducing those cells to become phagocytic.

DR. TENENBAUM: No.

DR. TENENBAUM: Do you know whether that is true or not.

DR. BHATNAGAR: No. The presence of phagocytosis has certainly a very different characterization of cells than what is happening here.

DR. TENENBAUM: If I can ask on a clinical matter, the radiographs that you showed, were the radiographs quantified at any point in the study?

DR. YUKNA: No, they weren't. It was not set up

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to do so. It was not intended in the beginning to do that, no.

DR. TENENBAUM: So, generally the radiographs weren't standardized.

DR. YUKNA: They were semi-standardized but they weren't quantified.

DR. TENENBAUM: Then one last question at this point, the difference between probing attachment levels and clinical attachment levels was non-significant and, yet, defect fill appeared to be significant. I always find this interesting. Could you comment and clarify for me and the Panel what the relevance between those two measurements is and reconcile this apparent difference?

DR. YUKNA: I will try. I think in this type of evaluation it is important to determine both the hard tissue changes and the soft tissue changes. You have to realize that with any periodontal therapy, especially surgical therapy, there is going to be a re-adaptation of re-attachment of the soft tissue to the tooth by some mechanism. It might be epithelium; it might be connective tissue. The attachment level, pocket depth and recession measurements are strictly soft tissue measurements of where the probe stops and that tissue is somehow adherent to the

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tooth. That does not necessarily reflect, and probably doesn't reflect in most research the actual changes in the bone. So the bone defect and its changes may not necessarily reflect where the soft tissue is at least initially or sequentially attached to the tooth. So, that is why there is a difference in the bone changes when they may not be reflective of the soft tissues. And that is pretty consistent in the periodontal literature.

DR. TENENBAUM: Can I have one follow-up to that? In regard to the bone tissue regeneration, I think that that is one issue. But the other issue I think pertains to periodontal ligament regeneration and actual reattachment. Do you have any data showing one way or the other whether there has been any gain in periodontal ligament attachment or connective tissue attachment?

DR. YUKNA: Not at this point, no. No, without doing histology, obviously, we wouldn't have that information. We are hopeful that we might be able to do histology in the future. We don't have that information now.

DR. TRUMMEL: Clarence Trummel. A couple of questions, this is a follow-up to Dr. Patters' question so I guess it is to Dr. Yukna, about the blinding. I just want

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to make sure I understand. There were three surgeons involved, one at each site. They did the operative procedure based on the random assignment of the defects. They placed the material. They did the reentry. But the clinical examination at reentry and just the clinical probing, that was done by someone who was not involved in the surgery, did not assist. Who were those individuals?

DR. YUKNA: At Dr. Krauser's center it was one of the dental assistants, Rene Kruse, who is actually the office manager so she really wasn't involved in the hands-on assisting at treatment. In Dr. Callan's center it was one of his hygienists who, again, was down at the end of the hall and was just called in when the occasion arose. At LSU it was one of our faculty members who, again, was not part of the treatment scheme. I was the surgeon in those cases and I got up and walked away and he came and measured and I came back and broke the code and did my thing, and that was it.

DR. TRUMMEL: And these were the individuals you calibrated --

DR. YUKNA: Yes, sir.

DR. TRUMMEL: -- at these centers. Thank you. Obviously, you have shown some differences between OsteoGraf

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with and without the P-15 in in vitro studies. Do you have any evidence, unpublished or anecdotal, that there is a difference between these two products clinically?

DR. YUKNA: No, and that was one of the difficulties in even thinking about using the "N" as a control. There really wasn't any information. We decided that in order to establish clinical utility we really had to match it against the gold standard, the demineralized freeze-dried bone. Certainly, compared to other HA materials, and this would fall in the same category, there was a quantum difference in the percent defect fill, relative defect fill and things like that.

DR. TRUMMEL: Historically speaking.

DR. YUKNA: Historically speaking, yes, but not directly that I know of.

DR. TRUMMEL: One last question, in the calvarial defect model, where I think you indicated there was greater ingrowth of bone, was this quantified in any way or was this a qualitative assessment from histology?

DR. TOFE: It was qualified statistically significant ingrowth. That data is in the PMA.

DR. STEPHENS: I have one question. I am Willie Stephens. I am wondering if the performance of

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OsteoGraf/N-300 is not known, what was the motivation for looking at this material with the P-15 before the performance of the N-300 material was known? In other words, we have this material with P-15 and without. I am curious as to why the performance of the material with the coating was looked at without the performance before we knew the performance of the material without it.

DR. TOFE: As I understand your question, why didn't we do this study with OsteoGraf/N first?

DR. STEPHENS: Correct.

DR. TOFE: Primarily what happens with the OsteoGraf/N and, again, the market dictates what happens but, in essence, the OsteoGraf/N had, if I can quantify it, 1.3% uses by periodontists, essentially very, very little, because what we were hoping to do in that pocket wasn't being seen in the marketplace per se. We realized that we had to do something to stimulate it, if we wanted to use a product like this, and we needed also a matrix, a matrix which basically was very similar to bone. Therefore, we chose the OsteoGraf/N matrix from the chemistry standpoint and it was an ideal matrix to put the P-15 on. But it really wasn't being utilized at all. The market was dominated by freeze-dried bone and surgical debridement.

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That is what the clinical practice was for this particular indication.

DR. STEPHENS: Was that a result of the fact that the performance of the material was unknown?

DR. YUKNA: If I can add to that answer, I think it kind of reflected a concern with basic HA materials. Even regular freeze-dried bone was overwhelmed by demineralized freeze-dried bone because of the presumption that BMP was there and was going to be released. We now know that presumption might have been an error, from recent work that shows that there probably isn't much and it varies from tissue bank to tissue bank. So, this material with the in vivo and in vitro information suggested it could give us a biological advance using what was an acceptable, on the market, 510(k) approved material as simply the matrix and, therefore, our gold standard was against the DFDBA to compare it because that is what most people had faith in and it would seem to have the most data from these types of studies.

DR. REKOW: Any other questions?

DR. JANOSKY: Janine Janosky. I would like to return to the calibration issue once again, and maybe this will put it to rest for us but let's see. I am looking at

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some data that are presented in terms of reliability for intra- and inter. It looks like this might be a 12-month technical report and data analyses. In light of the comments that you have made today, it looks like calibration was done with the project director with each of these ancillary staff at each of the three sites. Am I correct in that?

DR. YUKNA: Yes.

DR. JANOSKY: Okay. If I look at most of the assessments, the reliability goes as low as 70% up to about 80, sometimes 90 but for the most part they are averaging about 80% in terms of reliability. Were assessments or calibration, namely reliability values, calculated among the raters themselves, not each of the raters with the project director?

DR. YUKNA: Yes --

DR. JANOSKY: They are calibrating to one project director --

DR. YUKNA: Right.

DR. JANOSKY: -- who is not actually performing any of the measurements.

DR. YUKNA: Right. Yes, we did at the initial one where everybody came to LSU. We did do among each other as

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well as against myself, and then repeated things and went over things to achieve consistency in the measurement scales. So, that was done both among them as well as compared to me directly at the initial calibration, and then was done individually at each center against myself, to repeat to make sure that the data was still in place.

DR. JANOSKY: But we don't have those data.

DR. YUKNA: No.

DR. JANOSKY: No, we don't? Okay. A follow-up to this question that would then lead me to another question. This is sort of a teetering question here. If I look at the way that you presented your reliability data, you are presenting concordance in terms of percentages for exact hits, and you are presenting concordance in terms of percentages for within 1 mm. The issue I have is if you are looking at reliability within 1 mm, isn't that your hypothesis? So, you are incorporating within the system of unreliability the exact difference that you are willing to say is clinically significant.

DR. YUKNA: Well, we listed that because, again, the norm in reporting this kind of information in periodontal literature is to report it both ways, exact concordance and within. So, the exact concordance was still

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close to 90% or high 80s. The other one was reported just for completeness, I guess. I don't know if that answers your question.

DR. JANOSKY: Not really. I am concerned because you are willing to accept 1 mm as unreliability in the way that the data are presented to me in terms of concordance. That also was the value that was used for clinical significance. So, really what is it? Is it clinically significance or is it just error in your measurement system? So that is sort of the issue that I can't get around. Can you help me sort of tease those two apart?

DR. YUKNA: I don't know --

DR. JANOSKY: No? Okay.

DR. REKOW: Can you go to a microphone, please, because the transcriber can't hear what you say, and identify yourself? Thank you.

DR. JEFFERS: Good morning. I am Barrett Jeffers, a consultant with CeraMed on this project. I have no relationships or conflicts of interest with CeraMed's stock.

I did not analyze any of the reliability data. That was primarily handled by the two biostatisticians at LSU. So, I am not going to be able to exactly answer the question that you have.

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DR. JANOSKY: I have just one other question, then I will leave some more for later, if that is all right. If I look at the way the trial was designed, you are actually looking at two different hypotheses. One is saying the test is as good as, and the other one is saying the test is better than.

When I look at the way the results are presented, I see new types of testing being incorporated that were not addressed in the way the trial was designed. So how can we lead to those conclusions? Namely, if you are comparing the test to the gold standard, the presentation today as well as the published material that I have is making statements about equivalence where the trial was designed to only say it was at least as good as. The other arm of the study is saying that it was better than and, again, I see this discrepancy between the way the study was designed with the results being reported and the conclusions being made. Can someone please address those two issues? You actually have two arms, one being the test with the gold standard, the positive, and the test with the negative control, and you have two different hypotheses for each of those, one saying at least as good as and the other one saying better than.

DR. YUKNA: I may not be understanding your

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question but semantically at least as good as and equivalence rings the same bell --

DR. JANOSKY: No, that is the issue that I am bringing up. No, they don't. They are two very different things.

DR. YUKNA: Then it was a matter of semantics or wording. You are right, we divided it into individual hypotheses but in order to consolidate treatment and make as efficient a study as possible, we felt we needed both the positive and negative control. So, the aim or the hypothesis was that the test material would be -- whatever term you want to use -- at least as good as or equivalent as the gold standard and better than surgical debridement, which is classic for this type of study. So, I don't know if I can answer your question.

DR. JANOSKY: Yes, I would like to revisit this a little later perhaps in the day, but maybe just one question -- well, clearly a few questions remain about this issue but what is it that you designed the trial to look at? Was it equivalence? Was it a betterment? And exactly did the data show that based on what you are presenting to us? You may not be able to answer that now.

DR. YUKNA: Let me just try. The primary

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hypothesis was equivalence to the DFDBA, and the trial showed that that happened, and more so. I mean, the data exceeded our expectations.

DR. JANOSKY: But the study was not designed to examine equivalence. Am I correct in that, in that initial design of the study?

DR. YUKNA: It was against the DFDBA.

DR. JANOSKY: Was it designed to look at equivalence or look at something at least as good as?

DR. YUKNA: Again, we can go around on this. To me, it means the same thing. If statistically it doesn't, I have to defer to someone else.

DR. JANOSKY: Okay. Perhaps later a statistician could address the issue. Thanks.

DR. GLOWACKI: I have a number of questions about the specificity of P-15's effect, and perhaps Dr. Bhatnagar can come back to the microphone. In the papers and abstracts that were submitted I didn't see some of the information that I recall you having presented many years ago when you were originally doing this work. I wonder if you can comment about control peptides because I think this is really where you started off. You cut the collagen up into little pieces. Yet, in the Qian and Bhatnagar paper I

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don't see a comparison against another peptide. Can you give us a little background about the importance of that particular amino acid sequence, whether a scrambled peptide would give similar effects upon attachment and DNA synthesis and proline synthesis for example?

DR. BHATNAGAR: I am going to answer that question first of all by identifying myself. I have followed the protocol. My name is Bhatnagar, and I am a professor at the University of California, San Francisco. I know Dr. Tofe but I have no financial interest or conflict of interest.

With that out of the way, I will answer your question, Dr. Glowacki. Yes, we did synthesize the peptide, in which the central IA sequence is the reverse to AI, and our main assay for biological activity is the ability of this peptide to inhibit the binding of cells to a collagenous matrix. If that does not work -- in other words, if the peptide does not inhibit the binding of cells to collagen we assume that that peptide isn't active, and we have been examining the activity of this IA reverse to IA peptide and we haven't found it to have any effect on the biological activity of cells. So, we have continued to use the IA as positive activity to assess its effect on cell behavior in the kind of matrices that we are looking at

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today.

DR. GLOWACKI: Can you clarify that for me? Because a peptide does or does not inhibit binding to collagen-coated dishes, does it mean to me obviously that that peptide would not attach to the ceramic hydroxyapatite particles, nor that it would have any influence?

DR. BHATNAGAR: No, it would have no influence on the biological activity of cells even if it is absorbed on the ceramic.

DR. GLOWACKI: Are there data showing that? Because what I am concerned about, you see, is that that assay was done in the absence of serum. It was a 24-hour assay. And whether those conditions are really specific enough for us to leap to a prediction for an in vivo effect by the P-15 peptide.

DR. BHATNAGAR: There was a good reason for not including serum in the binding assays that we looked at, and that is, fibronectin interferes with binding to the same sort of receptors. So, we wanted to look at the effect directly of the peptide. Secondly, the assays of cell binding that you saw in that paper with Qian and myself, that was, indeed, a short-term assay but we were looking at the ability of P-15 to adsorb, mobilize on the surface of

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hydroxyapatite to bind cells.

DR. GLOWACKI: So, in that particular assay did you examine the IA versus AI containing peptides?

DR. BHATNAGAR: Yes.

DR. GLOWACKI: But that is not published in the paper. And I wonder what your response would be to the question about the definition of migration, and whether you have, in fact, shown an effect by P-15 on migration of cells in vitro?

DR. BHATNAGAR: Yes. My definition of migration depends on migration, the kind of substrate. You know, frequently people talk about migration in terms of hemotaxis, for instance. Hemotaxis occurs across a gradient or concentration of soluble material. In the case of collagen that does not apply because collagen is an insoluble material. Movement on collagen occurs as a something climbing on a power pole, and I can describe P-15 as being a staple on the surface of the collagen fiber. Now, P-15, we have computed essentially forms as a kind of staple on the surface of hydroxyapatite as well and these cells try to maximize contact with the matrix as soon as possible. They do seem to adhere to this thing and then they migrate.

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We have experiments that are not part of this presentation here where we have examined migration of cells on titanium rods coated and not coated with P-15. We find that there is a tremendous difference. These titanium rods are placed vertically in a culture system where the cells are at the bottom, and we look at the movement of these cells and we have found that in 3 days cells will migrate about 4.5 mm because that is how long the rod was.

DR. GLOWACKI: Thank you. I think to me, and to most cell biologists, migration would mean some kind of a linear change in position. Again, not to nit-pick but I want to be very, very careful that I understand exactly what it is that you believe you have shown in the preclinical studies; that you are talking about the spreading of the cell over the HA particle being increased if there is P-15 adsorbed to the particle.

DR. BHATNAGAR: Yes.

DR. GLOWACKI: Not movement towards the particle.

DR. BHATNAGAR: No, not movement towards to the particle, but attachment and then spreading out and stretching.

DR. GLOWACKI: Thank you very much. That is a terrific picture. Your arms helped to explain it.

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(Laughter)

DR. AMAR: Dr. Bhatnagar, can I just follow-up with one question?

DR. REKOW: You have to identify yourself.

DR. AMAR: Salomon Amar, from Boston University. You mentioned earlier to Dr. Tenenbaum that the cells in contact with OsteoGraf/CS-300 expressed alkaline phosphatase.

DR. BHATNAGAR: Yes, sir.

DR. AMAR: I wonder what the genetic profile would be where there was still calcium expressed in contact with just plain OsteoGraf/N-300. What would be the behavior of those dermal fibroblasts in contact with the plain hydroxyapatite. That is the first question.

DR. BHATNAGAR: Yes.

DR. AMAR: And the second one, was there any attempt to culture dermal fibroblasts on only P-15? I will tell you what I am getting at, it is to ascribe exactly the role of the P-15 to this process.

DR. BHATNAGAR: Those are the two questions?

DR. AMAR: Yes.

DR. BHATNAGAR: The answer to the first question about alkaline phosphatase, it has been shown by others as

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well that when a variety of fibroblasts are cultured dermal fibroblasts are able to generate a certain amount of alkaline phosphatase. What we have shown is that this is a very large increased generation of alkaline phosphatase. In addition to that, we do see the induction of a number of bone related genes, such as osteonectin and osteopontin and others, as a result of the presence of P-15 on this material. The results are always compared to the hydroxyapatite without P-15.

DR. AMAR: So basically the profile is completely different if you were to culture dermal fibroblasts on plain hydroxyapatite.

DR. BHATNAGAR: Yes.

DR. AMAR: And what is the profile of dermal fibroblasts cultured on only P-15?

DR. BHATNAGAR: P-15 has to be immobilized on a surface. The closest I can come to answering that question is that we have grafted P-15 on polyester and when we grew dermal fibroblasts on polyester they did not undergo the same kind of changes. They did not express alkaline phosphatase or osteonectin, osteopontin. So that was something specific to hydroxyapatite matrices.

DR. REKOW: Not being a biochemist, I am sure that

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I am losing some of the nuances that are going on here, but I want to remind the Panel that while it is tempting to get into all sorts of interesting mechanisms of what is going on, this is supposed to be safety and efficacy and not the basic mechanism. So, I don't mean to offend any of the Panel members and I know that I don't understand some of those nuances so, please, continue to ask the questions but make sure that they address the problem that we are here and not things that are more appropriate in a scientific session for basic science.

DR. GLOWACKI: I have a question because understanding the terminology and the claims, it is very, very important for us to be very rigorous about what actually has and has not been shown, and what perhaps you have other information.

I think I would like to give Dr. Bhatnagar an opportunity to fully expand on that last answer because from the information that I saw in the published manuscript of Qian and Bhatnagar, I didn't see a correction for cell number and this is sort of the dilemma in doing the basic science study and then answering a particular question that leads one to think that something else may have been stated. In the study -- correct me if I am wrong -- with regard to

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the differences in alkaline phosphatase on the HA and HA plus P-15, there were no data that could exclude the possibility that that was because there were different cell numbers seeded and, therefore, different numbers of cells at the 7-day time point when you measured the alkaline phosphatase. Is that not an accurate statement?

DR. BHATNAGAR: That is an accurate statement.

DR. GLOWACKI: Thank you.

DR. BHATNAGAR: But could I explain?

DR. GLOWACKI: Please.

DR. BHATNAGAR: The results were quite dramatically different. If you look at the stain photograph, alkaline phosphatase staining occurred very early in the cells around the hydroxyapatite particles when there was no P-15. But in the case where there was hydroxyapatite with P-15 there was a very large increase in the staining pattern and the stain extended beyond -- specifically, there was a great deal more staining in the bridges between the particles. Therefore, they must be involved in the isometrics. Thank you.

DR. REKOW: Are there other questions at the moment? Yes, Dr. Jordan?

DR. JORDAN: Mine are a little more basic. I am

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wondering about comfort. Do you have any pre and post data in terms of were there post infection rates and were there pre and post clinical symptoms that you could evaluate?

DR. YUKNA: Yes, there were no untoward tissue reactions, infections or any other surgical complications with any of the treatments. There were some slight irritations after surgery, as is normal in some patients, but that was not selective to one or the other treatments. So, there was absolutely no difference. It seemed like a very innocuous material. Obviously demineralized freeze-dried bone is because it has been used so much, and the CS-300 is very similar.

DR. GLOWACKI: I have another clinical question, and forgive my naivete. There is a Ph.D. after my name! I was wondering about the wide age range in this group that was examined because I was a bit concerned, I guess, about the standard deviations and, actually, the under-whelming performance of the gold standard, the positive control, in this particular study because I think many of the statistical comparisons failed to show a difference between the curettage and the demineralized freeze-dried bone, which was not, I think, what you expected. I think that that may in part have been due to the "n". But I wonder if there

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were other clinical variables that may have accounted for that being such a wide range with regard to the positive control.

DR. YUKNA: I am not sure I understood. You started asking about the age and then you went to something. What is your question?

DR. GLOWACKI: The first part of the question is do you have any explanation for the fact that your positive control did not perform statistically significantly better than the debridement alone in all of the parameters that were your outcome measures?

DR. YUKNA: No. That was sort of a surprise, but that is why you do research. In reality, if you really look at our research in periodontics and you analyze the handful of studies that I showed that actually do this work of intra-patient, you know, self-controlled, there are minimal differences.

The other problem is that there is some inconsistency in the source of demineralized freeze-dried bone. I mean, I have two papers that showed that the source varies greatly in the amount of BMP that might be expressed, the osteogenesis that may be expressed even though it was often the same patient, the same lot, the same batch etc.,

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and may not have been as good as some other tissue banks material, although this tissue bank has a long history of successful use.

So, I can't explain it fully, except that I think it is probably more clinical reality than has been reported in the past. I have been involved in this type of research for 25 years now and the supposed BMP that is in the DFDBA, as we use it clinically from commercial tissue banks, probably does vary greatly. In this particular study that might have been the case. But that was also fairly consistent with all the patients.

You mentioned that the "n" might not be sufficient. You know, the "n" initially was calculated for the changes we expected to 22. We eventually got approval to take in up to 40, expecting some dropouts. We had at least 30 patients to evaluate. I think the results are very consistent among centers. There was no center by treatment effect, etc. So, I think that that is just the way this study turned out. It was a little bit of a surprise but not a complete surprise to me.

DR. GLOWACKI: Back to my comment about age, this really may reflect my clinical naivete so I would ask you to answer this both in the light of your clinical experience,

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as well as whether a post facto analysis of this particular study was done, and because of the wide age range, I guess from 35 to something into the 70s, whether an age analysis revealed whether the demineralized freeze-dried bone showed a wider than expected standard deviation, and whether the study could be improved upon by using patients that are more narrowly defined.

DR. YUKNA: Well, that is possible. It was set up to test about periodontitis, which means that there is only a lower age limit for that in our literature, and an analysis was not done as far as age is concerned, post hoc was not done. In reviewing the data, the consistency is really kind of impressive, especially for the CS-300 and kind of for the middle of the road response of the DFDBA.

DR. TENENBAUM: Just a couple of other clinical questions. I couldn't quite tell from what I read or what you presented, was it possible that one single patient, because of the code being opened, could have had all 3 sites treated with the same material? How was that done?

DR. YUKNA: Well, the code had a sequence. Depending what the code was, the lowest number got treatment A, B or C and all 3 treatments were to be applied to that patient. So, the randomization table that we had told us at

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the time that the surgical debridement and everything was ready for the grafting, then the measurements were taken by the blinded examiner and then the code was broken. Those materials were applied by the clinician, closed up and that was it. So, I guess that answers your question. The 3 defects had to receive 3 different treatments.

DR. TENENBAUM: So each code packet would be indicate a sequence.

DR. YUKNA: A sequence, yes. Also, the lowest number tooth might be very commonly a posterior tooth and, to avoid that, the randomization had all kinds of permutations on the 3 treatments.

DR. TENENBAUM: One of the issues that I think is quite laudable is the fact that you did the root preparation and all soft and hard tissue preparation before you knew what material was going on. So, I think that is a very laudable design feature.

One question I have, you mentioned in your presentation -- not in the presentation, in the documentation I think that although the examiners were blinded, when the treatment site was evaluated on reentry there was some potential for unmasking because you could see particles. Do you have any idea as to what percentage of

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times the examiners were, in fact, unblinded because they could see particles?

DR. YUKNA: No. They were asked just to measure and not pay attention to anything else. Obviously, you know, you can see particles but they would not know necessarily whether those were CS-300 or DFDBA particles. I mean, I don't think they had the clinical expertise to judge that. So, their level of involvement was just to go in and measure, and we tried to restrict that. But in any of these types of studies where you can see something, a particle, a membrane or something, you can't be completely blinded. That is why the independence of those examiners was key. They were not involved in the surgery and the surgeon left the area. And the documentation of what was done was not there; there was a separate data sheet. So, they had no way to look back and see, even if they wanted to. The three of them really didn't care at the time.

DR. TENENBAUM: So, then there was no information recorded one way or the other whether particles may have been DFDBA or HA.

DR. YUKNA: No, not when they measured. They had a clean data sheet without any code as to what was done in those areas. Just, this is where you need to measure these

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sites around these teeth.

DR. REKOW: Dr. Amar?

DR. AMAR: I think that credit must be given to the designer of this clinical trial which tremendously reduced patient variability in all the three treatments, and I must give the proper credit for that because it reduced tremendously patient variability which exists, particularly in the complex process of periodontal disease.

However, I just have a quick question with respect to the clinical analysis and clinical measurements done in the study. You know that when we add gingival recession for clinical attachment gain and residual pocket, we usually end up with a measurement of presurgical pockets. So when I went to the summary of the application in Table 2, I did this calculation for the OsteoGraf and it worked pretty well; on the DFDBA it worked pretty well. My question is, it doesn't work pretty well with the debridement.

DR. YUKNA: You are talking about the soft tissue?

DR. AMAR: Yes, the presurgical pockets --

DR. YUKNA: Right. Well, if you take the presurgical probings with 5.2 and the post-surgical -- whether you take the 6 months or 12 months it doesn't make any difference really -- 3.6, that is a difference of about

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1.5.

DR. AMAR: When I add up the post-surgical pockets, which is 3.6, plus 1.5 plus 1.1 in gingival recession and the gain of attachment is 0.1, I add up with 4.8 on average and the presurgical pocket is 5.2. So, is that the variation and the standard deviation?

DR. YUKNA: It could be. You know, we obviously tried to check these but I would have to say yes. You know, I would have to say that that was the case.

DR. AMAR: Do you see what I am getting at?

DR. YUKNA: Yes, I do, sir.

DR. AMAR: Because my concern is regarding the amount of gain in clinical attachment in the debridement. Are you comfortable with 0.1 mm?

DR. YUKNA: Comfortable or not, that is what it said. So, you know, I have no way of commenting on whether I am comfortable or not because that is what the data showed. In general we tend to see a little bit better. I agree with you.

DR. AMAR: Let me just make sure that I congratulate the company, and particularly the design of this clinical trial, with respect to reducing tremendous patient variability.

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DR. REKOW: Yes, Dr. Tofe?

DR. TOFE: One comment for Dr. Glowacki on the demineralized freeze-dried bone. As you appreciate, there is a variety in the "inductive" capacity of freeze-dried demineralized bone as a function of age. In this particular study the patients were chosen sort of right in the middle of the group so it wasn't only the young patient or the elderly patient.

DR. GLOWACKI: Are you referring to the donor?

DR. TOFE: Correct. The second point being that there was a lot of effort made to be sure that it was aseptically processed to get around any possible issue or concern with terminal sterilization and its impact upon BMP or any type of inductive capacity. So, it is somewhere in the middle.

DR. GLOWACKI: Yes, I don't think any of us know what that means with regard to biological activity. But it was all one batch?

DR. TOFE: Correct.

DR. GLOWACKI: Which is excellent design as well.

DR. REKOW: If there are no more burning questions perhaps we could go on to Dr. Betz' presentation. Then we will have an opportunity to come back and chat some more

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with you. Dr. Betz is a dental officer and scientific reviewer for the Dental Branch and he has some words that he would like to give us. Dr. Betz?

FDA Presentation

DR. BETZ: I was supposed to present this afternoon so I will just read my speech as presented because it is afternoon.

(Slide)

Good afternoon. For those of you who were not at last November's Dental Products Panel meeting, I would like to introduce myself. My name is Bob Betz. I am a reviewer in the Dental Branch of ODE, and a diplomate of the American Board of Periodontology. Today, FDA wishes to hear your thoughts and concerns regarding the approval of P960051, CeraMed's OsteoGraf/CS-300.

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The sponsors of OsteoGraf/CS-300 have described the device, the clinical study, and provided other information for you to consider. My presentation today will briefly touch on the device description as presented on the device label; the intended use as presented in the device labeling; the clinical study submitted to support this application; the FDA concerns; and our questions for the

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Panel.

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The product labeling for this device states that OsteoGraf/CS-300 is a natural hydroxyapatite that is radiopaque, of high purity, and contains a synthetic peptide known as P-15. In their submission the sponsor characterized this peptide and submitted animal and laboratory studies that demonstrate the cell attracting abilities for P-15. There was one human study submitted, the 31 patient, 3-treatment arm study conducted by Dr. Yukna and co-workers.

The sponsor markets OsteoGraf/N-300 under a 510(k) clearance. The only difference between the two, N-300 and CS-300, is the presence of P-15.

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Device labeling states that OsteoGraf/CS-300 particles are intended to be used for the treatment of infrabony osseous defects due to moderate or severe adult periodontitis. Volume 1, Number 1 of The Annals of Periodontology states that grafting materials like hydroxyapatite are believed to act as space fillers. Scaffolding, space maintenance, and the contribution of minerals for bone metabolism have also been proposed.

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The clinical study submitted to support this application was executed well, but had two major deficiencies. Final PMA review identified a few minor deficiencies as well.

The study submitted had three treatment arms: surgical debridement, which is the negative control; decalcified freeze-dried bone allograft, the positive control; and, of course, OsteoGraf/CS-300, the experimental arm.

DFDBA is still considered to the gold standard against which other periodontal treatments of this nature are compared. Surgical reentry in the study occurred at 6 months, and a clinical evaluation was conducted at 12 months. Clinical results were favorable for CS-300, and other results were within the broad range of measurements expected for the other two modes of treatment. FDA felt that an additional treatment arm could have been included in the study to compare OsteoGraf/CS-300 to OsteoGraf/N-300, the device without P-15. This treatment arm would support claims related to the addition of P-15 to the hydroxyapatite.

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The sponsor has stated that the letters "CS" in the name of this device stand for "cell stimulating." We are concerned that this claim may not be substantiated by the data submitted. We are also concerned about the substantiation of claims related to the clinical utility or clinical effectiveness of P-15. At this time, we are able to compare CS-300 to DFDBA. We are then able to compare DFDBA to other HA grafting materials but not within the same study.

FDA does not wish to imply that everything must be known about each and every mechanism of action before this or any other device or product before they may be placed on the market. We do know, however, that we have little experience with P-15 in human periodontal subjects. FDA needs your input as to whether data is sufficient to establish both safety and effectiveness for this device.

In addition, FDA believes that medical and dental practitioners do read labels. We hope they do. We were concerned about an implied claim for the presence of P-15 in CS-300 as compared to N-300 and other HA grafting products on the market. There must have been a reason for this inclusion. The FDA believes that the presence of P-15 on the label implies that it is there to perform a function,

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and that this function may establish a claim. This claim may need more justification than what has been presented.

On the patients selected for this study, with the calibrations performed for this study, and with the control measures executed within this study, we do not know how well CS-300 would far compared to N-300. Taking into consideration the criteria for study inclusion and exclusion, and variability of measurement in periodontal studies of this nature, we were concerned about the study sample size being representative of the patient population into which this device may be implanted.

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We, therefore, post the following questions for the Panel discussion and comment:

Question number 1, does the Panel believe that using the letters "CS" in this device name establishes a cell stimulation claim for the device?

Question number 2, does the Panel believe that the stated presence of P-15 establishes a claim, whether implied or direct, of clinical utility or clinical effectiveness for this device?

Regardless of your responses to questions 1 and 2, we would like you to answer the following questions:

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Number 3, is the fundamental study design appropriate to establish the safety and effectiveness of CS-300 as labeled, including all claims, such as cell stimulation, restoration of lost bone and so forth?

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Question number 4, are the indications and claims for this device supported by sufficient data to demonstrate the safety and effectiveness of this device?

Number 5, does the Panel feel that the study sample size is sufficient to represent the patient population into which this device is to be implanted?

Finally, number 6, does the Panel have other recommendations to address outstanding issues or concerns, such as labeling recommendations, pre or post approval studies, modification of device claims and so forth?

Thank you very much. That is it.

DR. REKOW: Thank you, sir. I think that we should break for lunch.

MR. SEIDMAN: May I make a statement before we break?

DR. REKOW: If you come to the podium, please, and identify yourself.

MR. SEIDMAN: I want to follow-up on Dr. Betz. I

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am Mel Seidman, FDA statistician who reviewed this application. There seems to be a lot of misunderstanding and concern about what they can or can't say, the sponsor that is.

So, I just want to reiterate what the design was, in my opinion. The design was based on a clinical measurement difference of at least 1.0 mm in clinical probing attachment level between the initial pretreatment measurement and a 6-month reentry measurement for the OsteoGraf/CS-300 treatment, and an estimated standard deviation of 1.1 mm for each mean value.

There are a couple of statements I would like to make. First, the sample size determination was correct, assuming a standard deviation and the minimum difference they wanted to detect. It was clinically valid. Assuming they are clinically valid, the sponsor, I think in my opinion, has shown this by the pocket depth reduction because they state that they all came from between 1.4 and 3.4. When they make claims though that a device is different between these groups, I don't believe they can do that because it wasn't designed to do that. The study was not designed to do that. All you can say is that the pocket reduction was a 1.0 mm difference from pre and post.

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So, I just wanted to state that. I think there has been some misunderstanding as far as what the sponsor is saying and what we are interpreting. I think it is good to analyze between the three groups and if there is a difference you can say there is a statistical difference. You can't say one is better than the other though. Thank you.

DR. REKOW: Thank you. See you in about one hour.

(Whereupon, at 12:25 p.m., the Panel adjourned for lunch, to reconvene at 1:40 p.m.)

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AFTERNOON SESSION

DR. REKOW: Now that we have our quorum, I will call you all back to order again, and the first order of business for this afternoon is presentations by the three Panel members. Then there is time for a review of specific questions that were raised by the FDA. Those questions that Dr. Betz raised are on the very last page that is in the folders for the Panel on the premarket approval, and it is also in your agenda.

Shall we go in the order as listed here? Dr. Trummel, are you ready to begin first, please?

Panel Presentations

DR. TRUMMEL: Yes. My concerns have largely to do with the implication that there is a benefit by coupling the P-15 protein to the hydroxyapatite material. That may well be, but my concern is that we don't have the validation of that. So, it comes down, I think, to an issue of design of the clinical trial and I think this is one of the questions that, obviously, was addressed by Dr. Betz. The question is does P-15 augment the bone fill regenerative capacity of the inorganic component of hydroxyapatite?

DR. REKOW: Do you have any other comments?

DR. TRUMMEL: No, not at this point. Thank you.

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DR. REKOW: Okay, Dr. Glowacki?

DR. GLOWACKI: I was asked to focus on the preclinical information. Having done that, I have similar concerns about the demonstration that P-15 has an additional effect in augmenting bone repair, over and above the hydroxyapatite.

I have prepared some written remarks, and for the benefit of the transcriber I think I will read them, starting off with the description of the product which I think we can skip.

This review concerns the preclinical information provided by the sponsor. By way of prologue, it is useful to point out that original basic science research articles are usually designed to report on experimental tests of specific hypotheses. Such documents are molded by authors, reviewers and editors to be of optimum interest to t he readership of the journals. Quality journals aim to publish innovative, rigorous mechanistic reports that pertain to issues of fundamental interest to basic and clinical investigators. Frequently, because of page restrictions and traditions in data presentation, the purpose of an article may not coincide with the kind of information needed to answer questions that arise during consideration of a PMA.

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In scientific investigations, the selection of control or controls depends upon the chosen null hypothesis and has impact upon warranted conclusions. Rephrasing this principle in the language of clinical devices and evidence-based medical practice, one would emphasize that claims for indications and performance of a device depends upon study design.

A number of documents were submitted to show effects of P-15, a synthetic peptide having 5 Gly-X-Y motifs, characteristic of the triple helical portions of collagen. One published paper on in vitro effects of the peptide P-15, an abstract from the 1997 IADR meeting, and 1 manuscript on in vivo studies were submitted as documentation of the properties of P-15. The paper by Qian and Bhatnagar, J Biomedical Materials Research, Volume 31, pages 545-554, 1996, describes the effects of increasing doses of P-15 on attachment of human dermal fibroblasts to anorganic bovine bone mineral particles, also known as OsteoGraf/N-300. Appropriate methods common to studies on cell attachment were employed to measure attachment.

I would like to discuss this paper in the light of the questions that will be posed to this Panel. First, the key result of this study is summarized in Figure 1, which

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indicates that 60% of the seeded dermal fibroblasts attached to control bone mineral within 24 hours, under the serum-free conditions of the experiment. At conditions where the mineral was saturated with P-15 peptide, the percent of attachment was increased from this baseline of 60% to approximately 87%. that, indeed, was a significant increase and shows that attachment to mineral can be enhanced by presoaking the mineral with solutions of P-15. the dose dependence of the attachment was shown with rigorous quantitative data. It is pointed out that addition of the peptide did not increase binding from zero, but that many fibroblasts do attach to the untreated mineral.

Two, cell binding studies can be done under serum-free conditions in order to remove attachment factors found in commonly used serum and to simplify analysis. The relationship between serum-free binding data to in vivo situations where one would expect to find serum and other tissue factors may limit extrapolation to clinical significance.

Three, the cells attach to the P-15-treated mineral appeared to have different morphology when cultured for an additional 7 days. Whether the difference, described as 3-dimensional layering around the particles, was

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attributable to the fact that there were more cells attached to the P-15-containing particles at the beginning of the experiment cannot be determined by these data. The study was just not designed to examine that question. I am under the impression that the cultures were continued in the absence of serum. This paper reports additional effects of the P-15, including increased clumping and cellularity by scanning electron microscopy, increased DNA synthesis by incorporation of 3H-thymidine, and increased protein synthesis by 14C-proline incorporation. Those data were not normalized for cell numbers and may, in fact, just be reflecting the differences in total cellularity in the two experimental groups. Nevertheless, there appear to be differences between the mineral particles with and without P-15. One possibility is that P-15 increases the number of cells in intimate contact with the particles where they are stimulated by the calcium in the particles. Cheung and collaborators have reported that many cell types will proliferate when grown on calcium-containing particles even in the absence of serum. These new data showing that P-15 enhances the ability of calcium-containing particles to support cellular proliferation are of fundamental interest to scientists investigating control of cell cycle. So the

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model that one could propose is that the P-15 attached to the surfaces of the calcium phosphate particles enhances the attachment of the cells to those particles and, therefore, they are in a good geographical proximity to be influenced by the collagen itself, as well as the calcium and phosphate within the particles.

Four, selection of human dermal fibroblasts was good because these are connective tissue cells of importance in wound repair. It was stated that they serve as a surrogate for osteoblasts because it had been reported by others that binding of fibroblasts and osteoblasts to collagen involve the same set of integrin receptors. That is a sound rationale, however, the implication that binding of the 2 cell types to mineral with and without the P-15 would need to be tested directly. It could be a disadvantage if a bone substitute material actually stimulated the ingrowth of fibroblasts at the expense of osteoblasts or preosteoblasts.

Five, the results in this paper concerning alkaline phosphatase were not quantitative but of interest. Whether this observation is an indication of osteoblastic differentiation of skin fibroblasts is not answered by this study. Another possibility is that calcium phosphate